

# *AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report*

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## **Priority Area 04: Dementia (Including Alzheimer’s Disease)**

**Prepared for:**

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## **Statement of Funding and Purpose**

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHS290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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## **Financial Disclosure Statement**

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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## Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: [effectivehealthcare@ahrq.hhs.gov](mailto:effectivehealthcare@ahrq.hhs.gov).

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# Executive Summary

## Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 600 topics are being actively tracked in the system.

## Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 170 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

## Results

The table below lists the single topic for which (1) preliminary phase III data for drugs (or preliminary late-phase clinical trial data for off-label drug indications) was available; (2) information was compiled and sent for expert comment before May 8, 2015, in this priority area; and (3) we received five to seven sets of comments from experts between July 1, 2014, and May 18, 2015. (Eighteen topics in this priority area were being tracked in the system as of May 8, 2015.) A single topic, listed below, was eligible for consideration in this report.

### Priority Area 04: Dementia (Including Alzheimer’s Disease)

Topic	High-Impact Potential
1. Off-label intranasal insulin for treatment of Alzheimer’s disease	No high-impact potential; archived on basis of expert comments

## Discussion

The National Center for Health Statistics rates Alzheimer’s disease (AD) as the sixth-leading cause of death among Americans. The nonprofit Alzheimer’s Association also has estimated that more than 5 million Americans were living with AD in 2013, including about 11% of Americans older than age 65 years and 32% of Americans aged 85 years or older. Despite the scope and severity of AD and other dementia disorders, the Healthcare Horizon Scanning system has identified relatively few non-diagnostic interventions within this priority area.

The neurobiological complexity of AD and other dementias continues to confound researchers and clinicians. In particular, research has not established a definitive cause or causes of AD, hindering innovations in diagnostics, pharmaceutical development, and patient management. Frustratingly, an unusually high percentage of investigational drugs have not met primary endpoints in late-stage trials, and many novel neuropsychological therapies have shown inconsistent efficacy with expanded usage; a July 2014 paper by Jeffrey Cummings and colleagues in the journal *Alzheimer’s Research & Therapy* reported that only 1.8% of investigational AD drugs were successful in phase III trials. As a result, the U.S. Food and Drug Administration has not approved an AD-treating drug since galantamine in 2004.

Recent basic research results suggest that beta- or gamma-secretase inhibitors or related precursor inhibitors could be a foundation for new, effective AD pharmacotherapies. Correspondingly, the Horizon Scanning System is tracking multiple potential therapies with these properties, including an investigational RAGE (receptor for advanced glycation endproducts) inhibitor and two BACE (beta-amyloid precursor protein site-cleaving enzyme) inhibitors; these three drugs are under investigation in phase II/III or phase III clinical trials.

Besides tracking topics formally, the leads for potential topics identified by the system's staff of daily scanners have pointed us to possible high-profile drugs and devices that are still in very early development. Among these interventions on the far horizon, perhaps the most widely discussed is aducanumab, an anti-beta-amyloid multimer antibody. The manufacturer considers the phase I data encouraging enough that it plans to advance directly to a phase III trial later this year. We continue to monitor early developments of new drug candidates and diagnostics in this priority area and will update this report as potential high-impact topics arise.

### **Eligible Topic Not Deemed to Have High Impact Potential**

- **Off-label intranasal insulin for treatment of Alzheimer's disease:** Investigators hypothesize that abnormal insulin signaling in the brain is a factor in AD etiology. Recent neurobiological studies have also linked certain co-localized neural insulin receptors and insulin-sensitive glucose transporters in AD progression. As a result, researchers have posited that treatments that safely increase insulin levels or insulin signaling efficiency might improve disease progression and reduce cognitive symptoms in patients with probable AD.

Intranasal insulin is a candidate intervention with these desired properties. This drug, in various formulations, is approved and widely used to manage diabetes indications; no major manufacturers are testing it for other indications, so its potential use for treating AD would be off-label. U.S. and European investigators are leading phase II and II/III clinical trials studying intranasal insulin for treating AD, including scientists at the Alzheimer's Disease Cooperative Study (La Jolla, CA), Wake Forest University (Winston-Salem, NC), and the Veterans Affairs Puget Sound Health Care System (Seattle, WA). Data are available from completed pilot studies and larger ongoing studies, but these publications have not clearly associated intranasal insulin administration with improved cognition in AD, nor have they established effective or maximum tolerated dosing protocols. As a result, the experts who commented on this intervention concluded that it lacks high-impact potential.

For a more detailed discussion of this topic, including a brief survey of outcomes data available through late 2014, please refer to the December 2014 Potential High-Impact Interventions report published on the AHRQ website.